UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/782,614	02/19/2004	Stefan Bekiranov	3583.1	6311

22886 7590 09/28/2006

AFFYMETRIX, INC
ATTN: CHIEF IP COUNSEL, LEGAL DEPT.
3420 CENTRAL EXPRESSWAY
SANTA CLARA, CA 95051

EXAMINER	
MILLER, MARINA I	
ART UNIT	**PAPER NUMBER**
1631	

DATE MAILED: 09/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/782,614	BEKIRANOV ET AL.	
	Examiner	Art Unit	
	Marina Miller	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *8/24/2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/17/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' submissions filed on 2/169/2004 and 8/ 24/2004 are acknowledged. Claims 1-6 are pending. Claims 1-6 presently are under examination. The following rejections and/or objections are applied.

Priority

Applicants' claim of priority to provisional applications 60/448,741 filed 2/19/2003 and 60/458,141 filed 3/26/2003 is acknowledged.

Information Disclosure Statement

Information Disclosure Statements (IDS) filed 6/17/2004 has been considered in full.

Drawings

The drawings are objected to under 37 CFR 1.83(b) because they are incomplete. Drawings 2 and 4 do not contain axis labels (*e.g.*, [I] v. [T]; ln[I] v. ln[T], *etc.*). Y-axis of drawing 1B is labeled "Franction Bound." For the purpose of the examination, examiner interprets this to be a typographical error, and the label is treated as disclosing "Fraction Bound." Appropriate correction is required.

37 CFR 1.83(b) reads as follows:

> When the invention consists of an improvement on an old machine the drawing must when possible exhibit, in one or more views, the improved portion itself, disconnected from the old structure, and also in another view, so much only of the old structure as will suffice to show the connection of the invention therewith.

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure

must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the examiner does not accept the changes, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-6 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claim 1 recites a method for predicting probe response comprising relating a sequence dependent parameter with probe response and predicting probe response for a value of the sequence dependent parameter. However, not all processes are statutory under 35 U.S.C. 101. *See Interim Guidelines for Examination of Patent Applications for Patent Subject Matter Eligibility.* 1300 O.G. 4, on 22 November 2005 (published at the USPTO web site http://www.uspto.gov/web/patents'patog/week47/OG/TOC.htm). To satisfy 101 requirements, the claim must be for a practical application, which can be met if the claimed invention "transforms" an article or physical object to a different state or thing OR the claimed invention otherwise produces a useful, concrete, and tangible result. If claims are directed to abstract ideas

(such as mathematical algorithms), natural phenomena, and laws of nature, the claims must be considered as a whole for determining whether abstract ideas, natural phenomena, or laws of nature have a particular application.

In the instant case, the claimed method does not transform or reduce an article or a physical object (*e.g.*, signals produced by labels) to a different stage or thing. Specifically, the claimed method recites mathematical and/or statistical manipulations with sequence parameters and probe response (*e.g.*, hybridization information). The claimed method does not transform or reduce an article or a physical object (*e.g.*, hybridization signals) to a different stage or thing because the "result" of the method (*i.e.*, predicted probe response) is merely data (hybridization information) and is not equivalent to physical transformation. The claims do not recite tangible expression (*i.e.*, real-world result) of predicting probe response. Thus, the method does not recite steps of producing something that is concrete, useful, and tangible, and is not statutory.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentations are "undue." These factors include, but are not limited to:

a) The breadth of the claims;
b) The nature of the invention;
c) The state of the prior art;
d) The level of one of ordinary skill;

e) The level of predictability in the art;
f) The amount of direction provided by the inventor;
g) The existing of working examples; and
h) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. 858 F.2d at 740. While all of these factors are considered, sufficient amounts for a prima facie case are discussed below.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising relating ΔG^* with ln(I)/ln(T) by establishing empirically ΔG^* and ln(I)/ln(T) using the Langmuir model, predicting ΔG^* using nearest neighborhood analysis and multiple linear regression analysis models, and predicting ln(I)/ln(T) from the established empirical relations, does not reasonably provide enablement for a generic method for predicting unknown probe response. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

a) Claim 1 generally recites relating an unknown sequence dependent parameter to an unknown probe response and predicting the response. However, the specification only discloses relating ΔG^* with ln(I)/ln(T) by establishing empirically ΔG^* and ln(I)/ln(T) using microarray data and the Langmuir model (p. 28-32); predicting ΔG^* using nearest neighborhood analysis and multiple linear regression analysis models, and further predicting ln(I)/ln(T) from established empirical relationships (p. 32-35); and evaluating the prediction by comparing predicted and observed values (p. 35). The instant specification does not provide specific guidance to practice

the invention because it does not disclose how to predict generic probe response related to generic sequence dependent parameters.

Claim 5 recites a model for predicting ΔG* which depends from a probe sequence. Claim 6 further recites that the model (*i.e.*, for predicting ΔG*) is established by relating intensity and target levels using the Langmuir model. However, the specification discloses that the Langmuir model is only used for relating ΔG* with ln(I)/ln(T), and not for predicting ΔG* (p. 28-32). The specification discloses the nearest neighbor analysis and multiple linear regression analysis models for predicting ΔG* which depends from a probe sequence (p. 32-34). The instant specification does not provide specific guidance to practice the invention because it does not disclose how to use the Langmuir model for predicting ΔG*.

b) The invention is drawn to a method for predicting probe response.

d) The skill of those in the art of molecular biology and bioinformatics is high.

c), e) The prior art analysis shows that thermodynamic parameters (ΔG*, T_m) are used for predicting probe response. *See* Lane, US 6,027,884; Hyndaman, *BioTechniques*, 20(6):1090-1096 (1996); Friend, US 7,013,221; McKendry, PNAS, 99(15):9783-88 (July 23, 2002). The probe response is determent by a slope of a curve ln(I)/ln(T). *See* Friend US 7,013,221 (col. 19-22); Burchard, US 6,171,794 (col. 14-15); Mei, WO 02/42485; Hunt, EP 1209612. Prior art also discloses using the nearest-neighbor model for predicting ΔG*. *See* Lane, US 6,027,884 (col. 12, lines 57-60); Hyndaman, *BioTechniques*, 20(6):1090-1096 (1996); Frient, US 7,013,221 (col. 20, lines 33-36). The analysis also shows using the Langmuir absorption isotherm model for fitting experimental data to derive relationships among thermodynamic parameters and a target. *See* McKendry, *PNAS*, 99(15):9783-88 (July 23, 2002).

f) The specification does not provide working examples and does not teach how to make and use a method without knowing what sequence dependent parameters and probe responses are used for the prediction. The specification also does not teach how to use the Langmuir model for predicting ΔG^*. The specification only discloses drawings exemplifying predicted and observed ln(I)/ln(T) (probe response) for two YTC genes and correlation coefficients, but does not disclose how the predicted and observed probe response (ln(I)/ln(T)) has been obtained for those genes (pages 35-36). The specification only discloses using the Langmuir model for establishing empirically relations between ΔG^* and ln(I)/ln(T).

h) In order to practice the claimed invention, one skilled in the art must randomly select a sequence dependent parameter and must guess which probe response to use for predicting the response. One must also guess how to use the Langmuir model for predicting ΔG^*. This constitutes undue experimentation.

Due to the undue experimentation required to obtain the goal of the invention, the lack of directions presented in the specification, the complex nature of the invention, and the state of the prior art showing using thermodynamic parameters for predicting probe response and the Langmuir model for relating probe parameters, the specification fails to teach one skilled in the art how to use the claimed method for predicting unknown probe response for an unknown sequence parameter.

Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites steps of relating a sequence dependent parameter with probe response and predicting probe response for a value of the sequence dependent parameter. It is not clear what specific steps of "relating" and "predicting" are intended and what criteria, models, and/or algorithms are used for "relating" and "predicting".

It is further not clear whether "a sequence dependent parameter" and/or "probe response" recited in the step of "relating" and "predicting" are empirical, predicted, or both. Specifically, the specification discloses extraction of ΔG^* and probe response from a microarray using a model (empirical data) on pages 28-32 and 35. The specification also discloses predicting ΔG^* using a different model and predicting probe response based on the model used for extracting empirical data on pages 32-35. As the intended limitations are not clear, claims 1-6 are indefinite.

Claim 3 recites the limitation "I is the intensity in a complex background and T is target level." It is not clear what "intensity" is intended, *e.g.*, intensity of a complex "probe:target", intensity of a complex wherein the intensity of a background is subtracted, intensity of unbound probes and/or target, *etc.* It is also unclear whether "a complex background" means the background intensity (*e.g.*, attributed to a noise) is subtracted from the intensity attributed to a target:probe complex OR multicomponet/composite (*i.e.*, complex) background. Neither the

specification nor the claim defines the limitation. As the intended limitations are not clear, claims 3-6 are indefinite.

Claim 6 recites the limitation "the model is established by relating intensity to target levels using ... the Langmuir ... model in experimental data in simple background ... to extract ... parameters." It is not clear whether the model is established to extract parameters OR the Langmuir model is used to extract parameters.

It is further unclear whether the model is established in experimental data in simple background OR the Langmuir model is used in experimental data in simple background.

It is also unclear whether the model is established by relating OR relating is performed by using the Langmuir model.

The limitation "simple background" is also unclear and neither the specification nor the claim defines the limitation.

It is also unclear whether "in experimental data in simple background" is intended to mean, for example, a background of the experimental data, a background subtracted from the experimental data, a sum of experimental data and a simple background, *etc.*

As the intended limitations are not clear, claim 6 is indefinite.

Claim 6 recites the limitation "wherein the model is established by relating intensity to target levels." It is not clear what specific steps of "relating" and "establishing" are intended and what criteria, models, and/or algorithms are used for "relating" intensity with target levels and "establishing" the model.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Burchard, US 6,171,794.

Burchard discloses determining thermodynamic parameters of the probe:target hybridization (col. 14, line 15 thorough col. 16, line 61; col. 26, lines 8-65; fig. 1, 5-8). Burchard discloses relating a sequence dependent parameter (ΔG) with probe response (*e.g.*, intensity of hybridization, kinetic parameters) (col. 26, lines 8-65; fig. 1, 5-8). Burchard discloses predicting probe response (*i.e.*, determining experimental and theoretical thermodynamic parameters, comparing the parameters, and selecting probes) (col. 14, line 15 thorough col. 16, line 61; col. 26, lines 8-65; fig. 1, 5-8). Specifically, Burchard discloses equations relating ΔG and, for example, intensity or kinetic parameters (col. 14-15 and col. 26, lines 8-65), wherein ΔG may be determined by theoretical models and experimentally. Burchard further discloses fitting theoretical and experimental results (col. 26, lines 8-65 and fig. 5-7). Thus, Burchard anticipates claims 1-2. Burchard discloses logarithmic relations between intensity and a target (fig. 5-7 and (col. 14, line 16 thorough col. 15, line 61; col. 26, lines 8-65; fig. 1, 5-8). Thus, Burchard

anticipates claims 3-4. Burchard discloses a theoretical prediction of ΔG using the nearest-neighbor model (col. 26, lines 20-26). Thus, Burchard anticipates claim 5.

Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Lane, US 6,027,884.

Lane discloses a method of hybridizing complementary single stranded molecules having a preselected value for a free energy parameter (ΔG) (*i.e.*, relating ΔG with probe response) (abstract, claim 1, col. 1, lines 40-67). Lane discloses predicting probe response for ΔG (col. 40, lines 45 through col. 43, line 10). Lane discloses comparing predictions with experiments (col. 42, lines 20-65). Lane discloses predicting ΔG using the nearest-neighbor model (col. 40, lines 45-65). Thus, Lane anticipates claims 1-2.

Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Hyndaman, *BioTechniques*, 20(6):1090-1096 (1996).

Hyndaman discloses determining an optimal oligonucleotide sequence based on the hybridization simulation (*i.e.*, predicting probe response) (abstract). Hyndaman discloses relating a sequence parameter (ΔG) and probe response (*i.e.*, probe hybridization parameters) (p. 1091 and fig. 2). Hyndaman discloses determining theoretically a free energy using the nearest-neighbor model (p. 1091, right col.). Thus, Hyndaman anticipates claims 1-2.

Claims 1-5 are rejected under 35 U.S.C. 102(a) as being anticipated by Rui, WO 02/42485.

Rui discloses relating a sequence parameter (*e.g.*, ΔG) with probe response (*e.g.*, intensity, kinetic parameters) (formulas on p. 15-16; p. 17). Rui discloses a computer method for predicting probe response (*e.g*, intensity of hybridization) and selecting nucleic acid probes (abstract, claims 1-2, fig. 18; example on pages 29-22). Thus, Rui anticipates claims 1-2. Rui discloses logarithmic relations between intensity and a target level and a slope of the response curve (p. 2, lines 5-11; p. 16), thus anticipating claim 3. Rui discloses establishing empirically the relation between ΔG and intensity (p. 17, lines 12-19, example on pages 29-31). Thus, Rui anticipates claim 4. Rui discloses a theoretical model for predicting ΔG (p. 16, line 19 to p. 17, line 5; table on pages 23 and 25). Thus, Rui anticipates claim 5.

Claims 1-5 are rejected under 35 U.S.C. 102(e) as being anticipated by Friend, US 7,013,21.

Friend discloses a method of a probe design (abstract). Friend discloses relating a sequence parameter (*e.g.*, ΔG) with probe response (*e.g.*, intensity, kinetic parameters) (col. 19-22; fig. 4; col. 9, lines 61-63; col. 9, line 61 through col. 10, line 42). Friend discloses predicting probe response (*i.e.*, obtaining theoretical and experimental thermodynamic data, comparing the data, and selecting probes) (col. 19-22). Thus, Friend anticipates claims 1-2. Friend discloses that probe response is determined by a slope of a logarithmic relation of intensity and a target level (col. 21-22), therefore anticipating claim 3. Friend discloses measuring a hybridization level for a fixed concentration of a target and determining binding energy from the slope of the line (col. 21, lines 20-35) (establishing empirically the relation between ΔG and probe response), therefore

anticipating claim 4. Friend discloses predicting ΔG using the nearest-neighbor model (col. 22, lines 22-31), therefore anticipating claim 5.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Friend, US 7,013,21, as applied to claims 1-5 above, in view of McKendry, *PNAS*, 99(15):9783-88 (July 23, 2002).

Friend teaches the method of claims 1-5, as set forth above.

Friend does not teach the Langmuir model for relating ΔG to intensity and a target level.

McKendry discloses a method of determining probe binding using thermodynamic parameters (p. 9783, right col.). McKendry discloses using the Langmuir absorption isotherm model for fitting concentration-dependent data into the model to derive thermodynamic parameters of hybridization (p. 9786, left col, and fig. 3).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method Friend to use the Langmuir absorption isotherm model for fitting concentration-dependent data, such as taught by McKendry, where the motivation would have been to establish empirically the relation between ΔG and concentration dependent parameters of hybridization, as taught by McKendry, p. 9786.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marina Miller whose telephone number is (571)272-6101. The examiner can normally be reached on 8-6, M-Thu.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, Ph. D. can be reached on (571)272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Marina Miller
Examiner
Art Unit 1631

MM

ANDREW WANG
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600